## REMARKS

Claims 1-37 are pending in the instant application. Claims 1-37 have been rejected by the Examiner.

By the above amendments, Claim 25 has been amended to correct a typographic error. Applicants submit that the amendments are fully supported by the specification as filed, and no new matter is being added. After entry of the amendments, Claims 1-37 will remain pending and under consideration.

Reconsideration of the captioned application based on the previous amendments and following remarks is respectfully requested.

Claims 16 and 31-37 have been rejected under 35 U.S.C. §102(b) as allegedly anticipated by Maryanoff et al. US 4,582,916.

Applicants respectfully traverse the rejection. Applicants submit that Claims 16 and 31 are each directed to a product by process, and Claims 32-37 are dependent from Claims 16 and 31. Applicants submit that Maryanoff et al., in US 4,582,916 do not teach or suggest the product by process of the present invention. Applicants further submit that the claims directed to a product by process are not substantial duplicates of claims directed to the composition of matter claimed by Maryanoff et al., as they are not so close in content that they cover the same thing/invention.

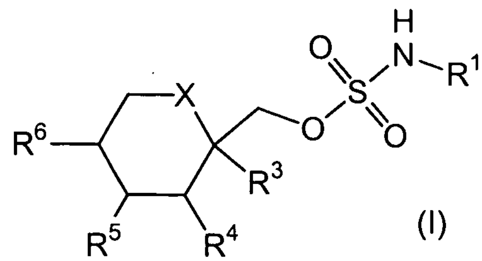
Applicants therefore respectfully request that the rejection of Claims 16 and 31-37 under 35 U.S.C. §102(b) be withdrawn.

Claims 1-37 have been rejected under 35 U.S.C. §103(a) as allegedly obvious over Maryanoff et al., US 4,582,916 taken with Maryanoff et al., US 5,387,700 in view of Hatt et al., Aust. Jol. Chem. Vol. 18 no. 12 pp 2045-2048 (1965).

More specifically, the Examiner states that Maryanoff et al., in US 4,582,916 teach the claimed pyran and cyclohexyl compounds, that Maryanoff et al., in US 5,387,700 teach analogous compounds made by a process in which a compound corresponding to applicant's formula (II) is reacted to form a compound corresponding to formula (I) and that

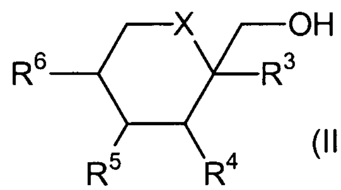
Hatt et al. teach an analogous process of reacting sulfamide and pyranose to obtain compounds of the same type as recited in the claims.

Applicants respectfully traverse this rejection. Applicants submit that the present invention is directed to a process for the preparation of compounds of formula (I)



(I)

comprising reacting a suitably substituted alcohol, a compound of formula (II)

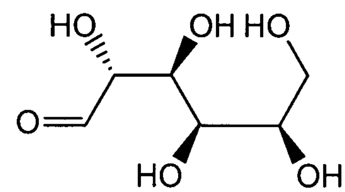


(II)

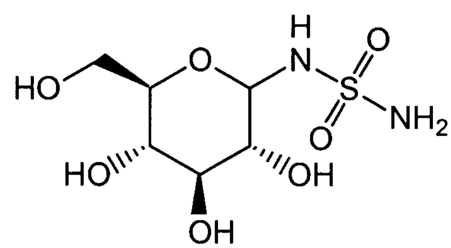
with sulfuryl diamide (sulfamide), at an elevated temperature, in the presence of from 0 to about 10% water.

Applicants submit that Maryanoff et al., in US 4,852,916 disclose a process for the preparation of compounds of formula (I) comprising reacting a suitably substituted alcohol (a compound of the generic formula R-OH) with sulfuryl chloride to form the corresponding chlorosulfate compound (a compound of the generic formula R-O-$SO_2$-Cl) and then reacting the chlorosulfate with a suitably substituted amine to yield the corresponding compound of formula (I). Maryanoff et al., in US 5,387,700 disclose the same process for the preparation of compounds of formula (I), comprising reacting a suitably substituted alcohol (a compound of the generic formula R-OH) with sulfuryl chloride to form the corresponding chlorosulfate compound (a compound of the generic formula R-O-$SO_2$-Cl) and then reacting the chlorosulfate with a suitably substituted amine to yield the corresponding compound of formula (I). Applicants maintain the neither Maryanoff et al., US 4,582,916 nor Maryanoff et al., 5, 387,700 teach or suggest reacting the alcohol of formula (II) with sulfamide to yield the corresponding compound of formula (I).

Further, Applicants submit that Hatt et al., in Aust. Jol. Chem. Vol. 18 no. 12 pp 2045-2048 (1965) (a copy of which is attached herewith for the Examiner's convenience) do not teach or suggest the process of the present invention. Hatt et al., disclose the reaction of glucose, mannose, galactose and fructose with sulphamide, wherein only the reaction of glucose and mannose with sulfamide yielded a product. (See, Hatt et al., page 2045, second paragraph) Further the process as disclosed by Hatt et al., is a condensation of the aldehyde group of the sugar with sulfamide, followed by cyclization of the intermediate product. The product prepared by Hatt et al., is a compound of the formula R-NH-$SO_2$-$NH_2$ rather than a sulfamide derivative of the formula R-O-$SO_2$-$NH_2$ as in the present invention. For Example, Hatt et al., disclose the reaction of glucose, a compound of the following formula



with sulphamide ($NH_2$-$SO_2$-$NH_2$) to yield β-D-glucopyranosylsulphamide, a compound of the following formula



Applicants submit that, by contrast, the process of the present invention comprises a displacement reaction, wherein the hydroxy group on the compound of formula (II) (a compound of the generic formula R-OH) is reacted with a suitably substituted sulfamide to yield the corresponding compound of formula (I) (a compound of the generic formula R-O-$SO_2$-$NR^1$). Thus Applicants maintain that Hatt et al., do not teach or suggest the process as claimed in the present application, and would not motivate one of ordinary skill in the art to conduct the instantly claimed process.

Applicants maintain that the teachings in Maryanoff et al., US 4,582,916, Maryanoff et al., US 5,387,700 and Hatt et al., Aust. Jol. Chem. Vol.18 no.12 pp 2045-2048 (1965), taken alone or in combination, do not render obvious the present invention and Applicants respectfully request that the rejection of Claims 1-37 under 35 U.S.C. §103(a) be withdrawn.

In view of the above remarks, Applicants maintain that the application is in condition for allowance and passage to issue is earnestly requested.

Respectfully submitted,

/Mary A. Appollina/

Mary A. Appollina
Attorney for Applicants
Reg. No. 34,087

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
(732) 524-3742
Dated: September 9, 2005

# GLUCOSYLSULPHAMIDE AND MANNOSYLSULPHAMIDE*

By H. H. Hatt† and A. C. K. Triffett†

Aldose sugars react with urea and with thiourea in the presence of acid to form glycosylureas and thioureas. Their reaction with sulphamide appears not to have been investigated previously and is now shown to lead to glycosylsulphamides. These compounds interested us as starting materials for the possible synthesis of sulphone analogues of nucleosides. (Naito *et al.*[1] describe analogous syntheses of nucleosides from glycosylureas.)

Glucose, mannose, and galactose reacted with sulphamide when heated in aqueous mineral acid and the course of the reaction was followed polarimetrically. Only glucosylsulphamide and mannosylsulphamide were obtained pure and crystalline: the first as a monohydrate, and the second in anhydrous condition. No evidence was obtained of a reaction between fructose and sulphamide; instead there was progressive destruction of fructose. With the aldoses in aqueous medium an equilibrium was reached between reagents and products at a composition which varied with conditions but always lay near 30% conversion to glycosylsulphamide. The presence in small amount of a second product, possibly the diglycosylsulphamide, was detected chromatographically, but was in no case isolated.

The reaction between glucose and sulphamide has been examined in greater detail. It took place slowly in absence of a catalyst when an aqueous solution of glucose and sulphamide was evaporated and then heated at 60° under reduced pressure. It was desirable to use acids to catalyse the reaction and the colour developed as a result of their use between 50° and 60° presented no difficulties. Boric acid proved the most suitable catalyst, if used under nearly anhydrous conditions at 50°, for there was then little development of colour and conversion could be raised to 40%. After most of this glucosylsulphamide formed had crystallized and had been removed, the mother liquors could be made to react further in presence of boric acid and in this way the isolation of 70% of total product was readily attainable. Under like conditions glucose and urea did not react.

Both glycosylsulphamides were very soluble in water and showed mutarotation without concurrent hydrolysis to the parent aldose. Both mutarotations were to more positive values and the crystalline compounds therefore presumably have $\beta$ configurations. The glycosylsulphamides are slowly hydrolysed by dilute mineral acid.

When glucosylsulphamide was oxidized with sodium periodate at 4° in darkness, there was rapid utilization of the periodate. In unbuffered solution 2 moles per mole of the sulphamide were consumed in 30 min and 3 moles in 2 hr. In 35 days 5 moles were consumed and the final pH was 1·0. When the reaction mixture was buffered

* Manuscript received June 24, 1965.
† Sugar Research Laboratory, CSIRO Chemical Research Laboratories, Melbourne.
1 Naito, H., Hirata, M., Kawakami, T., and Sano, M., *Chem. Pharm. Bull., Tokyo*, 1961, **9**, 703.

with sodium acetate–acetic acid at pH 4 the consumption of 2 moles of periodate took 3 hr, but the final extent of overoxidation differed little from that in unbuffered medium. The much less easily hydrolysed glucosylurea needed 24 hr for consumption of 2 moles of periodate and used a total of 3 moles in 35 days. Sulphamide itself did not react with periodate under like conditions.

The formic acid produced in the unbuffered oxidation was determined by titration. One mole had formed when two moles of periodate had been used and two when three had been used. Formaldehyde was first detectable by the chromotropic acid reaction after 24 hr by which time more than 3 moles of periodate had been consumed; thereafter the colour increased in intensity. This behaviour towards periodate demonstrates the presence in glucosylsulphamide of a pyranosyl ring.

## *Experimental*

Infrared measurements were made on an Infracord 137 spectrometer. Melting points are as observed on a Kofler melting point apparatus. Analyses are by the Australian Microanalytical Service, Melbourne.

### *β-D-Glucopyranosylsulphamide*

(i) *Preparation with sulphuric acid as catalyst.*—Sulphamide (2·4 g) (prepared according to the method of Goehring *et al.*[2]), and glucose (4·5 g) were dissolved in 1% aqueous sulphuric acid (10 ml) and heated at 60° for 96 hr. Barium carbonate was then added to the pale brown liquid in excess and, after filtering and decolourizing with a little charcoal, the liquors were concentrated under reduced pressure to a solids content of about 75%. The first crystals of *glucosylsulphamide monohydrate* formed after this syrup had stood for a little more than 2 weeks. When inoculation was possible the syrup became a crystalline magma in two days. The crystals were collected and washed thrice with 70% aqueous ethanol. Yield 1·8 g (26%).

(ii) *Preparation with boric acid as catalyst.*—Sulphamide (9·6 g), glucose (18 g), and boric acid (0·36 g) were dissolved in water (20 ml) and the solution evaporated under reduced pressure to a solids content of 80–85%. The syrup was heated in a vacuum oven at 50°, in which was placed a container filled with phosphorus pentoxide. After 80 hr water (40 ml) was added and the boric acid was removed with Amberlite Resin IR400(OH). The liquid was freed of resin, decolourized with charcoal, and concentrated to 75% solids content. Crystallization as in (*a*) gave 9·2 g of glucosylsulphamide.

When the mother liquors were mixed with boric acid (0·3 g) and the above procedure repeated, a further crop of glucosylsulphamide (6·2 g) was obtained. A repetition with the second mother liquors and boric acid (0·25 g) gave 4·1 g of glucosylsulphamide: in all 19·5 g (70%).

(iii) *Properties of β-D-glucopyranosylsulphamide.*—Paper chromatographic examination of the reaction products from either method of preparation revealed the presence of a small amount of a second product. A mixture of ethyl acetate, pyridine, and water in the volume ratio 3 : 1·25 : 1·0 was found most suitable for use in ascending chromatography. The spots were detected by means of silver nitrate in aqueous acetone followed by development with alcoholic alkali. Glucosylsulphamide then showed as a white spot surrounded by a dark halo ($R_G$ 165) and the unknown compound as a like spot at $R_G$ 70. They contrasted with the dark spot for unchanged glucose. The second compound has not been isolated, but could be diglucosylsulphamide.

The solubility of glucosylsulphamide is small in most organic solvents. It can be crystallized from 70% aqueous ethanol, but was best first freed of glucose and sulphamide by crystallization

[2] Goehring, M., Heinke, J., Malz, H., and Roos, G., *Z. anorg. allg. Chem.*, 1953, **273**, 200.

from one-third its weight of water, followed by washing with 70% aqueous ethanol. Some two-thirds was recovered in a crystallization. The colourless plate-like crystals were those of a monohydrate and melted over a range of 85–95° with partial loss of water and the formation of a compact glass from which the remaining water was slowly removed under reduced pressure. Complete dehydration was effected more rapidly by prolonged heating at 78° under reduced pressure. The anhydrous material was obtained only as a hygroscopic glass which dissolved in water and gave the crystalline *hydrate* again on concentration. Initially the hydrate had $[\alpha]_D^{20}$ $-4\cdot5°$ (*c*, 15·0 in water), but there was slow mutarotation and after 140 hr rotation was constant at $[\alpha]_D^{20}$ $+7\cdot7°$ (Found: C, 26·4; H, 5·8; N, 9·9; O, 46·3; S, 11·7; loss on drying, 6·6. $C_6H_{14}N_2O_7S,H_2O$ requires C, 26·1; H, 5·8; N, 10·15; O, 46·35; S, 11·6; $H_2O$, 6·5%).

The presence of glucose could not be detected by paper chromatography in the fully mutarotated solution, the pH of which was 6·2. However the compound was hydrolysed by dilute mineral acids and in solution in cold 0·1N sulphuric acid the presence of glucose was soon detectable by chromatography, and after 15 hr the spot intensity was consistent with about 10% hydrolysis. In a year, solutions in 0·2N sulphuric acid, initially the one 0·4M to glucose and to sulphamide, and the other 0·4M to glucosylsulphamide became identical. In agreement with this ease of hydrolysis, glucosylsulphamide reduced hot Benedict's and Barfoed's reagents in a few minutes, whereas under like conditions glucosylurea remained inert. The infrared spectrum of a paraffin-oil mull showed maxima below 1000 $cm^{-1}$ as follows: 940s, 925s, 910sh, 885s, and a broad strong band at 770 $cm^{-1}$. There was a strong band at 1650 $cm^{-1}$, but no other selective absorption up to 2000 $cm^{-1}$.

*Tetraacetyl* N-*β*-D-*Glucopyranosylsulphamide*

A solution of glucosylsulphamide (1·5 g) in pyridine (7 ml) was cooled to 0° and acetic anhydride (5 ml) added with stirring. After 24 hr the mixture was poured onto ice (15 g). The tetraacetate is appreciably soluble in water and the use of larger amounts of ice made necessary its recovery by extraction with chloroform. The *tetraacetate* separated as an oil which crystallized; yield, 1·5 g. Crystallized from 8–10 parts of hot water it formed colourless laths. These most often melted at 146–147°, but on occasion a second, presumably enantiotropic, form appeared, m.p. 167–168°, which reverted in the course of a few hours to the stable form of lower melting point. This had $[\alpha]_D^{20}$ $+23\cdot0°$ (*c*, 4·9 in $CHCl_3$). The infrared spectrum of a paraffin-oil mull showed an absorption band at 3700m attributable to unbonded $NH_2$ and a band at 3300 $cm^{-1}$ attributable to NH; one band at 1750s and no band at 1650 $cm^{-1}$. Bands below 1000 $cm^{-1}$ were present at 950m, 910s, 890m, and 880m with a broad band at 720 $cm^{-1}$ (Found: C, 39·5; H, 5·3; N, 6·5; S, 7·6; Ac, 41·5. $C_{14}H_{22}N_2O_{11}S$ requires C, 39·5; H, 5·2; N, 6·6; S, 7·5; Ac, 40·4%).

The tetraacetyl compound separates from a solution in chloroform in well-developed prisms of a *molecular addition compound* which loses its solvent of crystallization at 80° under reduced pressure (Found: C, 33·6; H, 4·3; N, 5·2; loss, 19·9. $C_{14}H_{22}N_2O_{11}S,CHCl_3$ requires C, 33·0; H, 4·3; N, 5·1; $CHCl_3$, 21·9%).

*Pentaacetyl* N-*α*-D-*Glucopyranosylsulphamide*

Powdered glucosylsulphamide (1·0 g) was added to a solution of zinc chloride (0·1 g) in acetic anhydride (5 ml) and warmed at 50° until dissolved, when the solution was cooled to room temperature. After 16 hr the mixture was poured onto ice, neutralized with sodium bicarbonate, and extracted with chloroform. When the washed and dried solution was freed of solvent 1·7 g of crystalline solid remained. Recrystallized from chloroform and light petroleum (40–60°) it formed small white *crystals*, m.p. 156–158°; $[\alpha]_D^{20}$ $+65\cdot2°$ (*c*, 5·1 in $CHCl_3$) without mutarotation. There was no absorption band in the infrared spectrum around 3700 $cm^{-1}$, but a strong band at 3300 $cm^{-1}$(NH). Two strong bands were present in the 1700 $cm^{-1}$ region at 1750 and 1710. In the region below 1000 $cm^{-1}$ medium bands were present at 980, 960, 920, 900 and 840 $cm^{-1}$. The band at 840 $cm^{-1}$ can be considered to denote an α-glucosyl configuration[3] and is consistent with the use of zinc chloride as catalyst for the acetylation (Found: C, 41·1;

[3] Jones, A. S., and Ross, G. W., *Tetrahedron*, 1962, 18, 189.

H, 5·1; N, 5·7; S, 6·8; Ac, 46·4. $C_{16}H_{24}N_2O_{12}S$ requires C, 41·0; H, 5·2; N, 6·0; S, 6·8; Ac, 45·9%).

*Mannosylsulphamide*

Mannosylsulphamide was prepared from an equimolecular mixture of mannose and sulphamide following method (*b*) in the preparation of glucosysulphamide. The crude product was purified by crystallization from 70% aqueous ethanol; yield, after one crystallization: 15%. *Mannosylsulphamide* was obtained as white needles of the anhydrous compound, m.p. 171–173° (dec.); $[\alpha]_D^{22}$ $-25\cdot0°$ (*c*, 5·0 in water). Its aqueous solution mutarotated slowly and attained a constant value of $[\alpha]_D^{22}$ $-7\cdot5°$ in 12 days. Mannose could not be detected by paper chromatographic means in the mutarotated solution (Found: C, 28·2; H, 5·7; N, 10·5; O, 43·6; S, 12·4. $C_6H_{14}N_2O_7S$ requires C, 27·9; H, 5·5; N, 10·85; O, 43·4; S, 12·4%).

*Tetraacetylmannosylsulphamide*

Mannosylsulphamide was acetylated with acetic anhydride and pyridine according to the method described for glucosylsulphamide. *Tetraacetylmannosylsulphamide* crystallized from 95% ethanol in colourless crystals, m.p. 193–195° (dec.) (Found: C, 40·1; H, 5·2; N, 6·2; Ac, 40·1. $C_{14}H_{22}N_2O_{11}S$ requires C, 39·5; H, 5·2; N, 6·6; Ac, 40·4%).

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Both glycosylsulphamides were very soluble in water and showed mutarotation without concurrent hydrolysis to the parent aldose. Both mutarotations were to more positive values and the crystalline compounds therefore presumably have $\beta$ configurations. The glycosylsulphamides are slowly hydrolysed by dilute mineral acid.

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[1] Naito, H., Hirata, M., Kawakami, T., and Sano, M., *Chem. Pharm. Bull., Tokyo*, 1961, **9**, 703.

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The tetraacetyl compound separates from a solution in chloroform in well-developed prisms of a *molecular addition compound* which loses its solvent of crystallization at 80° under reduced pressure (Found: C, 33·6; H, 4·3; N, 5·2; loss, 19·9. $C_{14}H_{22}N_2O_{11}S,CHCl_3$ requires C, 33·0; H, 4·3; N, 5·1; $CHCl_3$, 21·9%).

### *Pentaacetyl* N-α-D-*Glucopyranosylsulphamide*

Powdered glucosylsulphamide (1·0 g) was added to a solution of zinc chloride (0·1 g) in acetic anhydride (5 ml) and warmed at 50° until dissolved, when the solution was cooled to room temperature. After 16 hr the mixture was poured onto ice, neutralized with sodium bicarbonate, and extracted with chloroform. When the washed and dried solution was freed of solvent 1·7 g of crystalline solid remained. Recrystallized from chloroform and light petroleum (40–60°) it formed small white *crystals*, m.p. 156–158°; $[\alpha]_D^{20}$ $+65\cdot2°$ (*c*, 5·1 in $CHCl_3$) without mutarotation. There was no absorption band in the infrared spectrum around 3700 $cm^{-1}$, but a strong band at 3300 $cm^{-1}$(NH). Two strong bands were present in the 1700 $cm^{-1}$ region at 1750 and 1710. In the region below 1000 $cm^{-1}$ medium bands were present at 980, 960, 920, 900 and 840 $cm^{-1}$. The band at 840 $cm^{-1}$ can be considered to denote an α-glucosyl configuration[3] and is consistent with the use of zinc chloride as catalyst for the acetylation (Found: C, 41·1;

[3] Jones, A. S., and Ross, G. W., *Tetrahedron*, 1962, **18**, 189.

H, 5·1; N, 5·7; S, 6·8; Ac, 46·4. $C_{16}H_{24}N_2O_{12}S$ requires C, 41·0; H, 5·2; N, 6·0; S, 6·8; Ac, 45·9%).

*Mannosylsulphamide*

Mannosylsulphamide was prepared from an equimolecular mixture of mannose and sulphamide following method (*b*) in the preparation of glucosysulphamide. The crude product was purified by crystallization from 70% aqueous ethanol; yield, after one crystallization: 15%. *Mannosylsulphamide* was obtained as white needles of the anhydrous compound, m.p. 171–173° (dec.); $[\alpha]_D^{22}$ $-25\cdot0°$ (*c*, 5·0 in water). Its aqueous solution mutarotated slowly and attained a constant value of $[\alpha]_D^{22}$ $-7\cdot5°$ in 12 days. Mannose could not be detected by paper chromatographic means in the mutarotated solution (Found: C, 28·2; H, 5·7; N, 10·5; O, 43·6; S, 12·4. $C_6H_{14}N_2O_7S$ requires C, 27·9; H, 5·5; N, 10·85; O, 43·4; S, 12·4%).

*Tetraacetylmannosylsulphamide*

Mannosylsulphamide was acetylated with acetic anhydride and pyridine according to the method described for glucosylsulphamide. *Tetraacetylmannosylsulphamide* crystallized from 95% ethanol in colourless crystals, m.p. 193–195° (dec.) (Found: C, 40·1; H, 5·2; N, 6·2; Ac, 40·1. $C_{14}H_{22}N_2O_{11}S$ requires C, 39·5; H, 5·2; N, 6·6; Ac, 40·4%).